

**AMENDMENTS TO THE CLAIMS**

1. (Currently Amended) A liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), said formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups [HG] said submicronic particles being non-covalently associated with at least one active principle (AP), wherein:

a dispersion medium of the suspension comprises water;

said formulation forms a gelled deposit *in vivo* when injected parenterally and;

wherein said formulation is at least partly caused by at least one physiological protein

present *in vivo*;

prolongs and controls the *in vivo* release time of the AP beyond 24 h after administration;

is liquid under the injection conditions;

and is liquid at the physiological temperature and [[/or]] at the physiological pH and [[/or]] in the presence of: a physiological electrolyte in a physiological concentration, and [[/or]] at least one surfactant.

2. (Previously Presented) The formulation according to claim 1, its concentration of [PO] is set at a value that allows the formation of a gelled deposit *in vivo* after parenteral injection, in the presence of at least one physiological protein.

3. (Currently Amended) A liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), this formulation:

a) being liquid in the ambient atmosphere;

b) being liquid at the physiological temperature and [[/or]] at the physiological pH and [[/or]] in the presence of:

a physiological electrolyte in a physiological concentration,

[[and/]] or at least one surfactant;

c) and comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups

[HG], said particles being non-covalently associated with at least one active principle AP, and the dispersion medium of the suspension comprises water,

its concentration of [PO] is set at a value that allows the formation of a gelled deposit *in vitro*, in the presence of at least one protein.

4. (Previously Presented) The formulation according to claim 1, wherein the concentration of [PO] is:

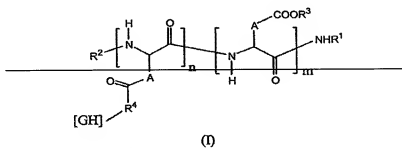
$$[\text{PO}] \geq 0.9.C1,$$

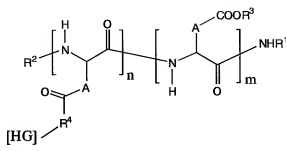
where C1 is the "induced gelling" concentration of the particles of PO, as measured in an IG test.

5. (Previously Presented) The formulation according to claim 1 wherein said formulation has a viscosity less than or equal to 5 Pa.s.

6. (Currently Amended) The formulation according to claim 1 wherein the [PO] is a polyamino acid formed of aspartic units ~~and/or~~ glutamic units, or both aspartic and glutamic units, at least one of said units carrying grafts containing at least one hydrophobic group [HG].

7. (Currently Amended) The formulation according to claim 6, the [PO] is defined by general formula (I) below:





in which:

R<sup>1</sup> is selected from the group consisting of: H, a linear C2 to C10 alkyl or branched C3 to C10 alkyl, benzyl, a terminal amino acid unit and -R<sup>4</sup>-[HG];

R<sup>2</sup> is selected from the group consisting of: H, a linear C2 to C10 acyl or branched C3 to C10 acyl group, a pyroglutamate and -R<sup>4</sup>-[HG];

R<sup>3</sup> is selected from the group consisting of: H and a cationic entity selected from the group consisting of:

metal cations selected from the subgroup consisting of sodium, potassium, calcium and magnesium,

organic cations selected from the subgroup consisting of:

cations based on amine,

cations based on oligoamine,

cations based on polyamine, and

cations based on amino acid(s) selected from the class consisting of: cations based on lysine or arginine,

and cationic polyamino acids advantageously selected from the subgroup comprising polylysine and oligolysine;

R<sup>4</sup> is a direct bond or a spacer based on 1 to 4 amino acid units;

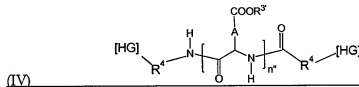
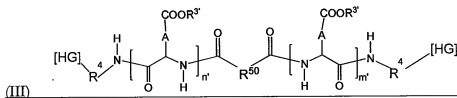
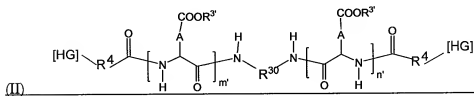
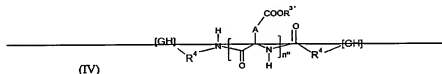
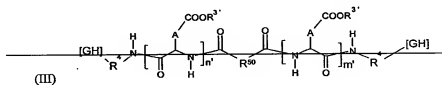
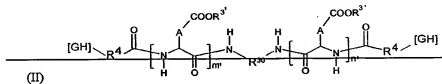
A independently is a radical -CH<sub>2</sub>- or -CH<sub>2</sub>-CH<sub>2</sub>-;

n/(n+m) is defined as the molar grafting rate and its value is sufficiently low for [PO], dissolved in water at pH 7 and at 25°C, to form a colloidal suspension of submicronic particles of [PO],

n + m varies from 10 to 1000 and;

[HG] is a hydrophobic group.

8. (Currently Amended) The formulation according to claim 6, the [PO] has one of general formulae (II), (III) and (IV) below:



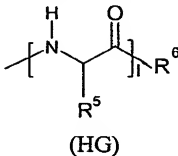
in which:

[HG] is a hydrophobic group;

R<sup>30</sup> is a linear C2 to C6 alkyl group;

- $R^{3'}$  is H or a cationic entity selected from the group comprising:  
metal cations selected from the subgroup consisting of sodium, potassium, calcium and magnesium,  
organic cations selected from the subgroup consisting of: cations based on amine, cations based on oligoamine, cations based on polyamine, and cations based on amino acid(s) selected from the class comprising cations based on lysine or arginine, and cationic polyamino acids selected from the subgroup comprising polylysine and oligolysine;
- $R^{50}$  is a C2 to C6 alkyl, dialkoxy or diamine group;
- $R^4$  is a direct bond or a "spacer" based on 1 to 4 amino acid units;
- A independently is a radical  $-\text{CH}_2\cdot$  or  $-\text{CH}_2\text{--CH}_2\cdot$ ;
- $n' + m'$  or  $n'$  is defined as the degree of polymerization and varies from 10 to 1000.

9. (Previously Presented) The formulation according to claim 7, the  $[\text{HG}]$  of the  $[\text{PO}]$  each independently of one another are a monovalent radical of the formula below:



in which:

- $R^5$  is a methyl, isopropyl, isobutyl, sec-butyl or benzyl;
- $R^6$  is a hydrophobic radical containing from 6 to 30 carbon atoms;
- 1 varies from 0 to 6.
10. (Previously Presented) The formulation according to claim 9, wherein at least one of the hydrophobic radicals  $R^6$  of the  $[\text{PO}]$  is independently selected from the group of radicals consisting of:
- a linear or branched alkoxy containing from 6 to 30 carbon atoms and of containing at least one heteroatom and/or at least one unit of unsaturation,

an alkoxy containing 6 to 30 carbon atoms, having one or more fused carbocyclic rings and containing at least one unit of unsaturation and/or at least one heteroatom,

an alkoxyaryl or an aryloxyalkyl having 7 to 30 carbon atoms and capable of containing at least one unit of unsaturation and/or at least one.

11. (Previously Presented) The formulation according to claim 9, wherein the hydrophobic radical  $R^6$  of the graft of the [PO] is derived from an alcohol precursor selected from the group consisting of: octanol, dodecanol, tetradecanol, hexadecanol, octadecanol, oleyl alcohol, tocopherol and cholesterol.

12. (Previously Presented) The formulation according to claim 6, the [PO] comprises of an alpha-L-glutamate or alpha-L-glutamic homopolymer.

13. (Previously Presented) The formulation according to claim 6, wherein the [PO] comprises of an alpha-L-aspartate or alpha-L-aspartic homopolymer.

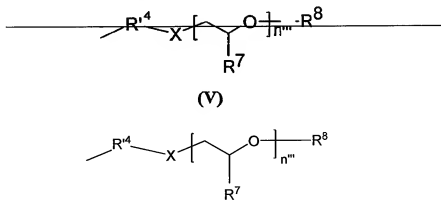
14. (Previously Presented) The formulation according to claim 6, wherein the [PO] comprises of an alpha-L-aspartate/alpha-L-glutamate or alpha-L-aspartic/alpha-L-glutamic copolymer.

15. (Currently Amended) The formulation according to claim 14, wherein, in the [PO], the distribution of the aspartic and [[/or]] glutamic units carrying grafts containing at least one [HG] unit is such that the resulting polymer is either random or of the block type or of the multiblock type.

16. (Previously Presented) The formulation according to claim 1, wherein the molecular weight of the [PO] is between 2000 and 100,000 g/mol.

17. (Currently Amended) The formulation according to claim 6, wherein the [PO] carries at least one graft of the polyalkylene glycol type bonded to a glutamate [[and/]] or an aspartate unit.

18. (Currently Amended) The formulation according to claim 17, wherein the graft of the polyalkylene glycol type has formula (V) below:



in which:

R<sup>4</sup> is a direct bond or a "spacer" based on 1 to 4 amino acid units;

X is a heteroatom selected from the group consisting of: oxygen, nitrogen and sulfur;

R<sup>7</sup> and R<sup>8</sup> independently are H or a linear C1 to C4 alkyl;

n<sup>m</sup> varies from 10 to 1000.

19. (Previously Presented) The formulation according to claim 17, wherein the polyalkylene glycol is a polyethylene glycol.

20. (Previously Presented) The formulation according to claim 17, wherein the molar percentage of polyalkylene glycol grafting varies from 1 to 30%.

21. (Previously Presented) The formulation according to claim 1 wherein, the hydrophobically modified [PO] are selected from the group consisting of: polyamino acids, polysaccharides, gelatins and mixtures thereof.

22. (Previously Presented) The formulation according to claim 1, wherein the AP is selected from the group consisting of: a protein, a glycoprotein, a protein bonded to one or more polyalkylene glycol chains, a polysaccharide, a liposaccharide, an oligonucleotide, a polynucleotide and a peptide.

23. (Previously Presented) The formulation according to claim 1, wherein the AP is a "small" hydrophobic, hydrophilic or amphiphilic organic molecule.

24. (Previously Presented) The formulation according to claim 1, wherein the weight fraction of AP not associated with the submicronic particles [non-associated AP], in weight %, is such that: [non-associated AP]  $\leq$  1.

25. (Previously Presented) The formulation according to claim 1 wherein the formulation is injectable by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour.

26. (Previously Presented) The formulation according to claim 1 wherein the formulation is used to prepare drugs for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route.

27. (Withdrawn -- Previously Presented) Process for the preparation of drugs, particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route comprising at least one formulation according to claim 1.

28. (Previously Presented) A derived product comprising submicronic particles formed of non-covalent PO/AP associations as defined in claim 1, and obtained from the formulation according to claim 1.

29. (Previously Presented) The derived product according to claim 28, said product is in a powder or a gel form.

30. (Withdrawn -- Previously Presented) A process for the preparation of the formulation of claim 1, said process comprising the steps of:  
taking a colloidal suspension of nanoparticles of at least one PO,



mixing this colloidal suspension of nanoparticles of PO with at least one AP, in aqueous solution, and  
adjusting the pH and/or the osmolarity if necessary.

31. (Withdrawn -- Previously Presented) A process according to claim 30, wherein the at least one AP is in the form of an aqueous suspension or solution for mixing with the colloidal suspension of nanoparticles of PO.

32. (Withdrawn -- Previously Presented) A process for the preparation of the formulation of claim 1, said process comprising the steps of:  
taking a powder of nanoparticles of at least one PO,  
mixing this powder with an aqueous suspension or solution of at least one AP, in aqueous solution, and  
adjusting the pH and/or the osmolarity if necessary.

33. (Withdrawn -- Previously Presented) A process for the preparation of the formulation of claim 1, said process comprising the steps of:  
taking a powder produced by drying the liquid formulation according to claim 1,  
mixing this powder with an aqueous liquid medium, and  
adjusting the pH and/or the osmolarity if necessary.

34. (Withdrawn -- Previously Presented) A process for the preparation of a powder derived from the formulation of claim 1, wherein said powder is obtained by drying the formulation of claim 1.